



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tetraacetythylenediamine (TAED): New Chemical Screen

EPA Identification Numbers:

P.C. Code:004115 MRID's: 45299702; 45712902; 45712903; 45274305;
45299704; 45547201; 45547202.
DP Barcode: D285497

TO: Dennis Edwards / Marshall Swindell/Tony Kish
Regulatory Management Branch I / PM Team 31
Antimicrobials Division (7510C)

FROM: Timothy F. McMahon, Ph.D. *[Signature]* 10/15/02
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THRU: Nader Elkassabany, Ph.D. *NE 10/15/02*
Acting Team Leader, Team Two
RASSB
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and

for Norm Cook, Chief *NE 10/16/02*
RASSB
Antimicrobials Division (7510C)

Action Requested: Perform a new chemical screen for registration of TAED as a technical grade active ingredient for non-food contact laundry disinfectant use with public health claims, non-food slimicide use in pulp and paper mills; reverse osmosis membrane systems; recirculating water in utilities/cooling towers/air washers; hydrostatic sterilizers/retorts/pasteurizers.

Background

This memorandum addresses the Toxicology data requirements for the proposed uses of this product. The Toxicology data requirements that apply to the registration of this new active ingredient for the intended uses are shown in the following table:

TOXICOLOGY DATA REQUIREMENTS FOR NON-FOOD USE
of TAED

TABLE 1

Guideline Number	Data Requirement	Have Data been submitted? ¹	MRID Number
870.1100	Acute Oral Toxicity	Y	45299702
870.1200	Acute Dermal Toxicity	Y	45712902
870.1300	Acute Inhalation Toxicity	N	waiver requested
870.2400	Primary Eye Irritation	Y	45299702
870.2500	Primary Dermal Irritation	Y	45299702; 45712903
870.2600	Dermal Sensitization	Y	45299702
870.3100	Subchronic Oral Toxicity	Y	45299703
870.3250	Subchronic Dermal Toxicity	Y	45274305
870.3700	Developmental Toxicity in Rats	Y	45299704
870.5265	Salmonella thyphimurium reverse mutation assay	Y	45547201
870.5375	Mucronucleus Test	Y	45547202
870.5395	Chromosome aberration test	Y	45547201

¹ Y = Yes; N = No

A waiver request for conduct of the acute inhalation toxicity study was submitted. This memorandum will determine the acceptability of the submitted data for review and will also determine the validity of the waiver request.

Conclusions/Recommendations

The submitted Toxicology data for new chemical screening of TAED has been examined using the acceptance criteria sheets as published within the Office of Pesticide Programs. The following conclusions are made:

- 1) The acute oral toxicity study did not report body weight measurements nor do they seem to have been measured. However, given that the estimated median lethal dose was above 5 g/kg, the study may be considered acceptable for review.
- 2) The older (1982) dermal irritation study is not acceptable for review. However, a newer study (MRID 45712903) was submitted and found acceptable for review.

3) The subchronic oral toxicity and subchronic dermal toxicity did not contain any assessment of motor activity, grip strength, or reactivity to sensory stimuli in the study design. The final OPPTS 870.3100 guideline for the subchronic oral toxicity and subchronic dermal toxicity tests were issued in 1998. The two submitted studies were conducted in the year 2000. As noted in the guideline, "Once, near the end of the exposure period and in any case not earlier than in week 11, assessment of motor activity, grip strength, and sensory reactivity to stimuli of different types (e.g., visual, auditory, and proprioceptive stimuli) should be conducted." Although the guideline also states that "Functional observations conducted towards the end of the study may be omitted when data on functional observations are available from other studies and the daily clinical observations did not reveal any functional deficits," there are no other studies with any functional observations in the submitted studies. It is unclear why these endpoints were omitted from the study design. In the absence of these measurements the registrant needs to be aware that if a determination is made that there is neurotoxicity evident in any of the studies and it is deemed to be of concern, additional studies on neurotoxicity may be required. These specific measures were not performed in either of these studies.

4) It is not clear from screening of the submitted Ames study that fresh cultures of bacteria in late exponential or early stationary growth phase were used in this study. The registrant should clarify this.

5) In the chromosome aberration test, a total of 100 metaphases were stated to have been scored per concentration, when the guideline requires a minimum of 200. An explanation is required.

6) The registrant requests a waiver for conduct of the acute inhalation toxicity study. The request is based on two areas: (i) the registrant claims that "potential exposure to TAED MP will only be: (a) at Warwick International's manufacturing facility during packaging by production workers; and, (b) at the formulation facility during un-drumming of TAED MP and its addition to enclosed powder mixing equipment. In addition, the registrant also claims that (ii) (a) "TAED-TGAI or TAED-MP contains essentially no particulate material in the respirable range, i.e. $\leq 10 \mu\text{m}$ in aerodynamic diameter. Therefore, it is eligible for an automatic waiver of this study requirement on the basis of lack of potential for inhalation exposure to TAED; (b) the total weight fraction percent of TAED-TGAI particles $\leq 10 \mu\text{m}$ in aerodynamic diameter was determined to be 4.78%; and (c) the total weight fraction percent of TAED-TGAI particles $\leq 10 \mu\text{m}$ in aerodynamic diameter was determined to be 0.25% of the fine fraction, $\leq 70 \mu\text{m}$, which is less than 1.0% of the total sample. The registrant conducted a particle size analysis using scanning electron microscopy and quantitative image analysis to report these values.

There is no information in the report to support the claim regarding lack of inhalation exposure. In fact, if the product were registered, it is quite likely that the scenarios mentioned could occur at more than one facility, involving many workers. There is also no mention of any respiratory protection for workers handling the product.

The registrant should also be aware that to obtain a waiver on the basis of particle size, they "must demonstrate that their product contains large, non-inhalable particles which are resistant to attrition." Attrition can occur during handling of the product, resulting in fines that are not only inhalable, but likely respirable. Lack of attrition can be demonstrated using ASTM Test Method 35.22-*Pesticide Formulations and Application Systems Method for the Determination of Inhalable Particles of Granular Products*. The registrant has arbitrarily used a value of 10 μm aerodynamic diameter as the respirable limit, but has not addressed inhalability. OPP is concerned about aerosol particles that can be inhaled into the respiratory tract. Particles are considered essentially non-inhalable if they are $>100\mu\text{m}$ in diameter.

The registrant has not supported the argument that there will be no inhalation exposure or that the particle size is not relevant to inhalation risk. The acute inhalation study waiver request is denied and the study must be performed.

D285494 - New Chemical Screen for tetraacetythylenediamine (TAED)

The registrant Warwick International Limited is requesting the registration of 5 TAED manufacturing use products: 59825-R (92%), -E (85%), -G (70%), -U (80%), and -L (99.5%). Two end-use product registrants are requesting the registration of two end use products: TAED + Na percarbonate - 16930-L, NorAm Tech Corp., "Wash and Bleach Extra"; and TAED + Na percarbonate - 1448-UEL, Buckman Laboratories, Inc., "Busan 1000".

TAED is tetraacetythylenediamine, Sha. Number: 059825.

Three ecotox studies were submitted in support of technical TAED. They are:

- 1.) MRID 452743-09, Acute Oral Avian Toxicity using the Bobwhite quail (OPPTS 850.2100),
- 2.) MRID 457129-01, Acute 48 hour *Daphnia magna* (OPPTS 850.1010).
- 3.) MRID 45743-08, Acute 96 hour Rainbow trout (OPPTS 850.1075).

These studies are acceptable for review (pass the screen).

Rick Petrie, 9/19/02

SUBJECT: Input for the 10/09/02 New Chemical Screen Meeting on a new active ingredient (a.i.), **TAED:Tetra-Acetyl Ethylene Diamine**, proposed for use as an industrial biocide and commercial/institutional hard surface disinfectant. Occupational exposure considerations regarding the *Warwick International Limited* registration applications for five manufacturing-use products (MUPs) ranging from 70 - 99.95% a.i.; and Human Exposure Data requirements for the use of **TAED** in two industrial/institutional end-use products (EPs) ranging from 11.76 - 33.33% a.i..

TO: Norm Cook, Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510C)

FROM: Doreen Aviado, Biologist *Doreen Aviado 10/2/02*
Team Two
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THRU: Nader Elkassabany, Team Leader
Team Two
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Antimicrobials Division (7510C)

DP
Barcode: D285259 (S620556)

Pesticide

Chemical(s)/ **MUPs:** Ethane, bis-1,2-([N,N-diacetyl]amino-) / 004115

No.(s): (Tetra-Acetyl Ethylene Diamine, *TAED*)

EPs: Ethane, bis-1,2-([N,N-diacetyl]amino-) / 004115 and
Hydrogen Peroxide (Sourced to Sodium Percarbonate) / 595

MRID No.: 452743-03

PURPOSE:

The purpose for conducting this "new chemical screen" is three-fold:

1) To conduct a new chemical screen of materials provided by the registrant, *Warwick International Limited*, to Product Management Team 33 (PM 33) in support of registration applications for five MUPs containing a new a.i., **TAED:Tetra-Acetyl Ethylene Diamine** [Ethane, bis-1,2-([N,N-diacetyl]amino-), PC Code:004115] intended for use as a technical source in formulating industrial biocide and commercial/institutional end-use products; and

2) To conduct a new chemical screen of materials jointly submitted by *Warwick International Limited* and the EP registrants, *Buckman Laboratories, Inc.* and *NorAmTech Corporation*, to PM 33 in support of registration applications for two industrial/institutional EPs containing a co-biocide mixture of the new a.i. **TAED** and a **Hydrogen Peroxide** source material (sodium percarbonate); also

3) To decide if enough data have been provided in the registrants' submissions to facilitate putting the packages into RASSB review for assessing any applicable Human Exposure Data requirements needing to be addressed.

BACKGROUND:

In support of registration for the five MUPs, as the a.i. technical source products, and the two formulated EPs, *Warwick International Limited* and the EP registrants, *Buckman Laboratories, Inc.* and *NorAmTech Corporation* provided administrative materials including transmittal letters, product labeling and CSFs, and data in support of any human exposure concerns the Agency may have regarding the occupational uses proposed for the new active ingredient (a.i.), **TAED**.

Registration applications have been submitted for the following proposed products:

EPA File Symbol	Product Name	% Active Ingredient(s)	Use Pattern
TAED MUPs:			
59825-L	Warwick B675 Industrial Disinfectant/ Biocide	99.95 % TAED	Formulator use in the manufacture of products intended as: 1) hard surface disinfectant commercial/institutional laundry detergents/warewashing detergents 2) pulp/paper mill slimicides 3) non-potable water treatment biocides for recirculating industrial water systems (recirculating cooling towers, heat exchangers, cooling water systems, reverse osmosis systems)
59825-R	Mykon AML Industrial Disinfectant/ Biocide	92.00 % TAED	
59825-E	Mykon ASD Industrial Disinfectant/ Biocide	85.00 % TAED	
59825-E	CX 1078 Industrial Disinfectant/ Biocide	80.00 % TAED (also for food-contact products manufacture)	
59825-G	CX 1071 Industrial Disinfectant/ Biocide	70.00 % TAED	
TAED EPs:			
1448-UEL	Busan 1000	33.33% TAED 18.15% Hydrogen Peroxide	paper mill/reverse osmosis/recirculating water systems
16930-L	Wash 'N Bleach Extra ²	11.76% TAED 7.32% Hydrogen Peroxide	commercial/institutional hard surface disinfectant laundry detergent

Human exposure data were provided by *Warwick International Limited* in the form of an occupational exposure report (MRID 452743-03) dated October 2, 2000, entitled "*TAED: Ethane, bis-1,2-([N,N-diacetyl] amino-) (A) Potential for Human Dietary Exposure Associated with Food Contact Hard Surface Disinfection (Potable Water Rinsed) and Food Contact Hard Surface Sanitizing (No Potable Water Rinse) (B) Potential for Human Dermal Exposure Associated with Laundry Disinfectant Uses.*" This report covers exposure estimates for Agency use in both dietary and non-dietary assessments and supports the proposed use patterns for the formulated EPs. In a broad sense the data addresses the Human Exposure Data requirements under Series 875 Guidelines. The submitted data are intended to characterize exposures for cooling water uses, commercial/institutional laundry disinfectant uses, commercial/institutional warewashing uses (food contact), surface sanitizer uses (food contact), and pulp/paper biocide uses (food contact). As a conservative screening tool the assessment includes quantitative dietary and dermal exposure dose estimates and calculated MOEs for the different commercial/industrial scenarios based on surrogate data from PHED.

RECOMMENDATIONS: A new chemical screen was conducted on the submitted materials for the intended use pattern and the following comments apply:

TAED MUPs:

- **FIFRA does not impose Human Exposure Data requirements for MUPs, only for typical EPs:** It is assumed that workplace safety standards set by OSHA for industrial manufacturing facilities and any specified personal protective equipment (PPE) are adequate to protect workers in contact with such chemicals;

TAED EPs:

- **The submitted data package was screened and can be put into review to support the EPs:** Based on the new chemical screen of materials/data provided by the registrants', *Warwick's* occupational exposure report (MRID 452743-03) submitted in support of the use of their **TAED MUPs** for formulating the *Buckman Laboratories, Inc.* and *NorAmTech Corporation* **EPs**, is adequate to be put into full RASSB review for addressing in general the Human Exposure Data requirements under Series 875 Guidelines.

The product labeling and data covered in the report will most likely fall under the minimum requirements for an EP (i.e., data to address GLN 875.1700 and 875.2700 *Product Use Information*, and GLN 875.2800 *Description of Human Activity* to better characterize the nature of the potential application/post-application exposures.) The quantitative exposure estimates in the report follows the Agency practice of accepting into review 'human health exposure risk assessments' for addressing any applicable Application and/or Post-Application Guideline Study requirements under GLN 875.1100/GLN 875.1200 *Dermal Exposure Outdoor/Indoor* and GLN 875.1300/GLN 875.1400 *Inhalation Exposure Outdoor/Indoor*.

- **The Agency reserves the requirement for submission of specific Series 875 Guideline studies in support of the EP registrations:** No additional human exposure data is required at this time. A determination will be made after RASSB has been able to fully review the submitted data package (MRID 452743-03), characterize the toxicological hazards, select appropriate endpoints, and conduct an occupational exposure assessment.
- In addition to registrant-submitted materials, when put into review, RASSB will refer to the occupational exposure assessment conducted for the December, 1993 *Peroxy Compounds RED* (which includes Hydrogen Peroxide and Peroxyacetic Acid) since the evaluation included specific precautionary labeling PPE statement requirements for products containing/generating peroxy compounds (i.e., protective clothing as mitigation for eye and skin hazards from handling products).
- The complete Human Exposure Data requirements applicable to the proposed industrial/commercial/institutional use patterns are provided below for future reference.

Antimicrobial Use Categories III: Commercial, Institutional and Industrial Premises and Equipment; and
VIII: Industrial Processes and Water Systems

Table 1. Human exposure data requirements - Application.

Data Requirements <u>Application</u> ¹	Guideline Reference		I. Old Practice	II. Current Practice	III. Proposed for Subpart W
	Old	New			
Product Use Information	none	875.1700	NR	² R	² R
Dermal Exposure Outdoor	231	875.1100 875.1600	CR	³ CR	³ CR
Dermal Exposure Indoor	233	875.1200 875.1600	CR	⁴ R	⁴ R
Inhalation Exposure Outdoor	232	875.1300 875.1600	CR	³ CR	³ CR
Inhalation Exposure Indoor	234	875.1400 875.1600	CR	⁴ R	⁴ R
Biological Monitoring	235	875.1500 875.1600	CR	³ CR	³ CR

Table 2. Human exposure data requirements - Post Application.

Data Requirements <u>Post-application</u> ⁶	Guideline Reference		I. Old Practice	II. Current Practice	III. Proposed for Subpart W
	Old	New			
Product Use Information	none	875.2700	NR	² R	² R
Description of Human Activity	133-1	875.2800	R	⁷ R	⁷ R
Indoor Surface Residue Dissipation	none	875.2300 875.2900	NR	⁸ CR	⁸ CR
Dermal Exposure	133-3	875.2400 875.2900	CR	⁹ CR	⁹ CR
Inhalation Exposure	133-4	875.2500 875.2900	CR	⁹ CR	⁹ CR
Biological Monitoring	235	875.2600 875.2900	CR	⁵ CR	⁵ CR

CR = Conditionally Required,
NR = Not Required,
R = Required.

Additional guidance is provided to data submitters as Guideline Reference No. 875.1600: Application Exposure Monitoring Data Reporting, and Guideline Reference No. 875.2900: Exposure and Risk Assessment Calculations.

FOOTNOTES:

¹ Application data are conditionally required when 1) based on the pesticide's toxicity certain toxicological criteria are triggered such as: Acute Toxicity Studies indicate Toxicity Category I for acute dermal and/or inhalation toxicity; and 2) the human activities associated with the pesticide use pattern can lead to potential adverse exposures to handlers (mixers/loaders/applicators).

² Product use information, where applicable, includes ranges and typical values for application rates, timing, methods, sites, frequency, equipment used, formulation types, and other relevant use data.

³ Required for outdoor uses when that is the primary use site, or if outdoor uses are expected to result in greater exposure than indoor uses.

⁴ Required to evaluate exposure to handlers for each intended use pattern:

commercial, institutional and industrial premises/equipment use pattern: application to hard surfaces (floors, walls, furniture, fixtures, etc.) in 1) commercial premises (e.g., hotels, motels, theatres, office buildings, airports, bus stations, train terminals, etc.); 2) institutional premises (e.g., schools, colleges, auditoriums, etc.); and 3) industrial premises (e.g., factories, mills, industrial plants, etc.); and,

industrial processes and water systems use pattern: 1) commercial/industrial processing water systems (e.g., cooling towers, evaporative condensers, air washers, heat exchangers, pulp/papermill systems, gas/oil recovery systems, wastewater and sewage systems etc.); and 2) specialized applications used in commercial/industrial processing water systems (e.g., immersion ultrasonic tank water, laboratory equipment water baths, photo processing wash water etc.).

⁵ Biological monitoring may be substituted in addition to or instead of dermal/inhalation exposure data, provided adequate pharmacokinetics data are available to interpret the biological monitoring data. Post application biological monitoring is required in cases where passive dosimetry techniques are not applicable for a particular exposure scenario, for example (but not limited to), swimming pools, hot tub baths, and showering.

⁶ Post Application data are conditionally required when 1) based on the pesticide's toxicity certain toxicological criteria are triggered such as: Acute Toxicity Studies indicate Toxicity Category I or II for acute dermal and/or inhalation toxicity; and 2) the human activities associated with the pesticide use pattern can lead to potential adverse exposures to workers upon reentry, and/or bystanders and residents.

⁷ Descriptions of human activity include exposure time per activity, type of protective clothing worn, application sites, activity patterns, and other relevant use data.

⁸ Required if the use pattern and formulation types involve significant potential exposure to humans by evaporation of residues from surfaces or contact with residues on treated surfaces. The surface residue study may be required in addition to dermal/inhalation data.

⁹ Testing for post application exposure would be needed unless the product use information and description of human activity, or chemical characteristics of the products in this category, indicate that exposure in and near areas where the pesticide has been applied is not likely to be significant.

Measurements of indoor inhalation exposure may be combined with tests discussed in OPPTS 875.1400.